[Chem. Pharm. Bull. 32(1) 44—54 (1984)]

Synthesis of *N*-Substituted (6-Benzyl-4,4-dimethyl-2-cyclohexenyl)-methylamines and Related Compounds[1)]

TAKESHI KATO,* KIYOHISA KAWAI, and YOICHI SAWA

Central Research Division, Takeda Chemical Industries, Ltd., Jusohonmachi, Yodogawa-ku, Osaka 532, Japan

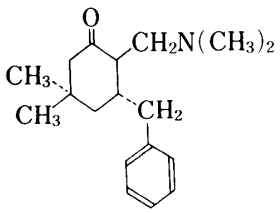
(Received May 6, 1983)

In a search for synthetic non-narcotic analgesics, 1,6-*trans*-*N*-substituted (6-benzyl-4,4-dimethyl-2-cyclohexenyl)methylamines (**5**) were prepared by dehydration of the corresponding 2,3-*trans*-2-aminomethyl-3-benzylcyclohexanols (**2** and **3**) with thionyl chloride. The (1-cyclohexenyl)methylamines (**4**) and the 1,2-*trans*-(2-chlorocyclohexyl)methylamines (**6**) were also produced from the 1,2-*cis*-cyclohexanols (**2**) as minor products, but the only isolable by-product from the 1,2-*trans*-cyclohexanols (**3**) was the 1,2-*cis*-(2-chlorocyclohexyl)methylamines (**7**). The 1,6-*cis*-(6-benzyl-2-cyclohexenyl)methylamine (**13a**) was obtained by isomerization of the 2,3-*trans*-3-benzyl-2-dimethylaminomethylcyclohexanone (**1a**) followed by reduction and dehydration. Catalytic hydrogenation of (2-benzyl-2-cyclohexenyl)methylamines (**17**) gave the 1,2-*trans*- and 1,2-*cis*-cyclohexylmethylamines (**8** and **19**). Among the compounds tested, 1,6-*trans*-*N*,*N*-dimethyl-(6-benzyl-4,4-dimethyl-2-cyclohexenyl)methylamine (**5a**) hydrochloride was as potent as codeine phosphate in analgesic activity as determined by the phenylquinone writhing method.

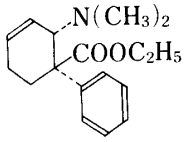
Keywords——non-narcotic analgesic; dehydration; configuration; thionyl chloride; cyclohexenylmethylamine; cyclohexylmethylamine; analgesic activity; chlorination

In a previous paper,[1)] we showed that 2,3-*trans*-3-benzyl-2-dimethylaminomethylcyclohexanone (**1a**) is almost equal to codeine phosphate in analgesic activity and that its potency is not enhanced by reduction of the carbonyl to a hydroxyl group.

Tilidine (A),[2)] reported to be a non-narcotic analgesic, has a cyclohexene structure with a *cis* configuration between the 2-dimethylamino and 1-phenyl groups. The structural similarity between **1a** and A led us to investigate the cyclohexene analogues (*i.e.*, **5**) and the *cis* isomers (*i.e.*, **13**) of type **1a** as potential analgesics.



1a



A

Chart 1

Synthesis of *N*-Substituted[6-Benzyl(and Phenyl)-4,4-dimethyl-2-cyclohexenyl]methylamines (5 and 13)

The cyclohexenylmethylamines (**5**) may be obtained directly by the dehydration of cyclohexanols (**2** and **3**) in the presence of an acidic catalyst. However, according to Saytzeff's rule,[3)] the undesirable compounds **4** would be preferentially obtained by acid-catalyzed

dehydration. We therefore investigated dehydrochlorination[4] of the chlorides (**6** and **7**) derived from the cyclohexanols (**2** and **3**).[1]

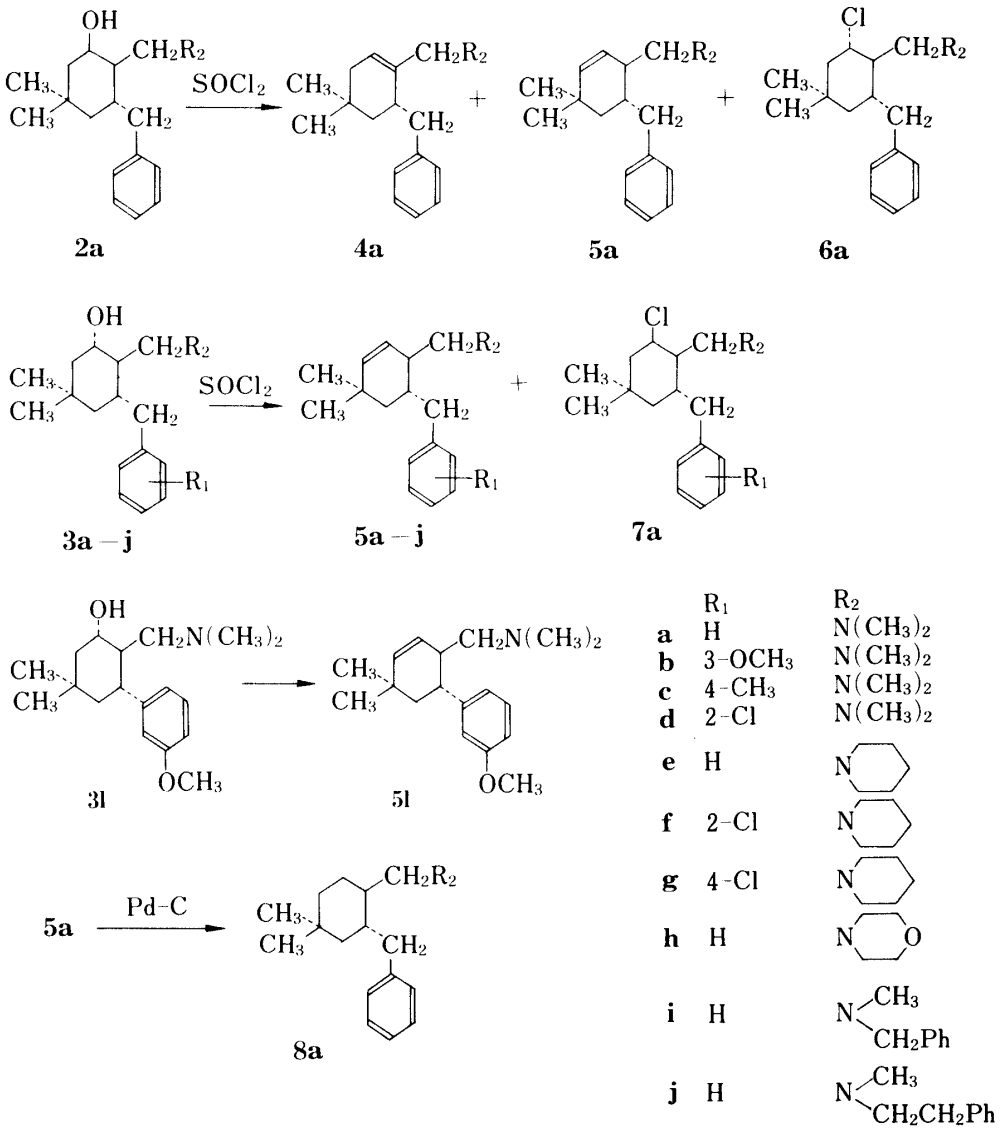
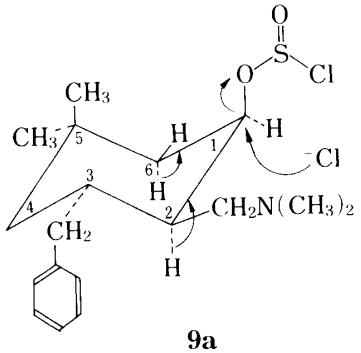


Chart 2

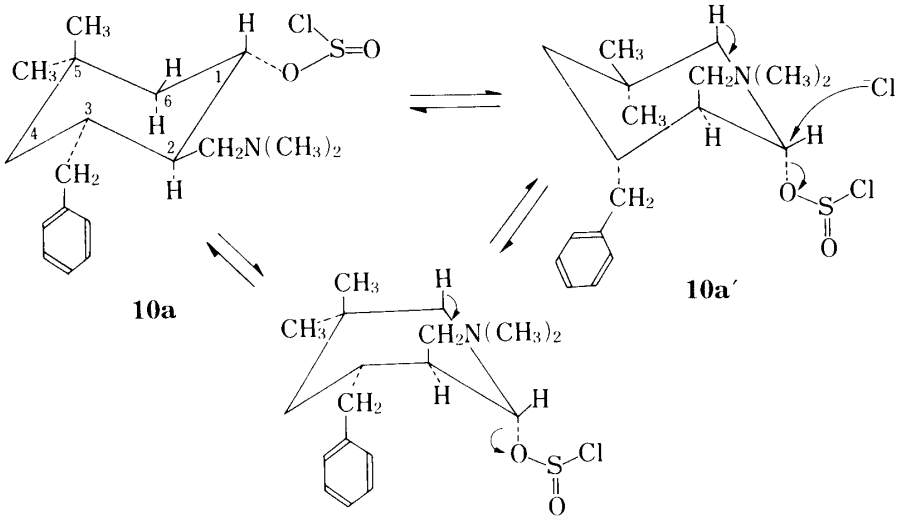
Treatment of *t*-3-benzyl-*c*-2-dimethylaminomethyl-5,5-dimethyl-*r*-1-cyclohexanol (**2a**) with thionyl chloride ($SOCl_2$) in dichloromethane gave *N*,*N*-dimethyl-(6-benzyl-4,4-dimethyl-1-cyclohexenyl)methylamine (**4a**) hydrochloride, mp 220—222 °C (dec.), as the major product in 38% yield. The desired *N*,*N*-dimethyl-(6-benzyl-4,4-dimethyl-2-cyclohexenyl)methylamine (**5a**) hydrochloride, mp 187—189 °C, and *N*,*N*-dimethyl-(*t*-6-benzyl-*t*-2-chloro-4,4-dimethyl-*r*-1-cyclohexyl)methylamine (**6a**), a colorless oil, were also obtained in low yields (14 and 18%, respectively).

Compound **5a** and the 1,2-*cis*-chloride (**7a**) were stereospecifically obtained in 75 and 19% yields, respectively, when the 1,2-*trans*-cyclohexanol (**3a**) was treated with $SOCl_2$; **4a** and **6a** were not formed in this reaction.

The structures of **4a**, **5a**, **6a**, and **7a** were determined on the basis of elementary analysis, and the nuclear magnetic resonance (NMR) and infrared (IR) spectra. In the NMR spectra, **4a** and **5a** exhibited signals due to the olefinic protons at δ 5.57 (1H) and δ 5.43 and 5.67 (2H), respectively. The methine proton at the C-2 position of **6a** appeared as an octet with coupling



9a



10a **10a′** **10a″**

Fig. 1

TABLE I. Chemical Shifts (δ) of One of the Methylene Protons of the Dimethylaminomethyl Group (in $CDCl_3$)

Compd.	C_1–C<H/H–N(CH$_3$)$_2$
5a	3.08 (1H, dd, J=3, 13 Hz)
6a	3.40 (1H, dd, J=3, 13 Hz)
7a	3.08 (1H, dd, J=9, 18 Hz)
8a	3.15 (1H, dd, J=3, 12 Hz)

constants of 5, 11, and 12 Hz at δ4.01 suggesting that the C_2–H is oriented in a *trans*-axial manner to the axial C_1–H. The C_2–H of **7a** appeared at δ4.65 as a quartet with a coupling constant of 4 Hz, which indicates that the C_2–H is oriented in a *cis*-equatorial manner to the axial C_1–H.

It is well known that the chlorination of an alcoholic hydroxyl group with $SOCl_2$ (an S_{Ni} reaction) proceeds with retention of configuration in the absence of a base, but with inversion of configuration in the presence of a base.[5] The reaction of **2a** and **3a** gave the chlorides (**6a** and **7a**) with inversion of configuration at C_1, probably because of the presence of the basic

aminomethyl group at C_2. Cyclohexene derivatives, **4a** and **5a**, might be produced *via* 1,2-*trans* and 1,6-*trans* elimination of the chlorosulfinyloxy intermediate (**9a**), respectively, since the chlorosulfinyloxy group becomes anti-coplanar with the axial protons at C_2 and C_6.[6] On the other hand, **5a** is selectively obtained from **3a** *via* the intermediate **10a′** or **10a″**, because only the 1,6-*trans* elimination of the chlorosulfinyloxy group is possible.

In the NMR spectra of **5a**, **6a**, and **7a**, characteristic signals corresponding to 1H were observed as double doublets at δ about 3.0—3.5 (Table I). A similar signal was also observed in the NMR spectrum of 1,2-*trans*-*N*,*N*-dimethyl-(2-benzyl-4,4-dimethylcyclohexyl)methylamine (**8a**) obtained by catalytic hydrogenation of **5a**. The signal (δ 3.40) of **6a** appeared at especially low field compared with the others (δ 3.08—3.15), so this signal was considered to be one proton signal of the methylene in a dimethylaminomethyl group (C_1–C$\overset{H}{\underset{H}{<}}$–N). Since this signal was not observed in the 1,6-*cis* cyclohexene derivative (**13a**) or 1,2-*cis* cyclohexane derivative (**19a**), as described later, the presence of this signal seems to be an index of the *trans*-orientation of the 2-aminomethyl and 3-benzyl groups.

1,6-*trans*-(2-Cyclohexenyl)methylamine (**5b**—**j**) hydrochlorides (Table II) were similarly obtained from the corresponding 2-aminomethylcyclohexanols (**3b**—**j**) *via* 2-aminomethyl-3-benzyl-4,4-dimethylcyclohexanones (**1b**—**j**).[1)]

1,6-*cis*-(2-Cyclohexenyl)methylamine (**13a**) was synthesized as shown in Chart 3. Compound **1a** was refluxed with 40% dimethylamine solution in order to convert the 2,3-*trans* form (**1a**) to the 2,3-*cis* form (**12a**), *i.e.*, we expected that isomerization of **1a** would occur on the readdition of dimethylamine to the demethylamine derivative (**11a**) produced under heating[7)] or on enolization (**11a′**). Reduction of the crude reaction mixture followed by

Table II. *N*,*N*-Substituted 2-Cyclohexenylmethylamines (**5**)

Compd.	mp (°C)	Recrystn. solvent[a)]	Yield (%)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
5b	160—162	A	13[c)]	$C_{19}H_{29}NO \cdot HCl \cdot 1/4H_2O$	69.47	9.39	4.26
					(69.46	9.19	4.25)
5c	157—158	A	12[d)]	$C_{19}H_{29}N \cdot HCl \cdot H_2O$	70.02	9.90	4.30
					(70.20	9.79	4.23)
5d	195—197	A	15[d)]	$C_{18}H_{26}ClN \cdot HCl$	65.85	8.29	4.27
					(65.38	8.46	4.22)
5e	239—243	A	36[d)]	$C_{21}H_{31}N \cdot HCl \cdot 1/5H_2O$	74.72	9.67	4.15
					(74.99	10.12	4.07)
5f	189—191[b)]	A	13[c)]	$C_{21}H_{30}ClN \cdot HCl$	68.47	8.48	3.80
					(68.46	8.46	4.01)
5g	238—239	B	24[d)]	$C_{21}H_{30}ClN \cdot HCl$	68.47	8.48	3.80
					(68.76	8.65	3.67)
5h	229—232[b)]	A	18[c)]	$C_{20}H_{29}NO \cdot HCl \cdot 1/5H_2O$	70.73	9.05	4.12
					(71.04	8.93	3.90)
5i	161—164	A	4.5[c)]	$C_{24}H_{31}N \cdot HBr$	69.56	7.78	3.38
					(69.54	7.73	3.18)
5j	184—186	A	35[c)]	$C_{25}H_{33}N \cdot HCl$	78.20	8.92	3.65
					(77.88	8.93	3.60)
5l	142—144	C	55[d)]	$C_{18}H_{27}NO \cdot HCl \cdot 1/5H_2O$	68.97	9.13	4.47
					(69.03	9.02	4.46)

a) A = AcOEt–MeOH; B = EtOH; C = AcOEt.
b) Decomposition.
c), *d*) Calculated from **1** and **3**, respectively.

dehydration gave **13a** in 12% yield. The NMR spectrum of **13a** showed the olefinic protons as a doublet and a complex doublet at δ 5.42 and 5.75, respectively; the mass spectrum (MS) showed the same fragment peaks as those of **5a**.[8]

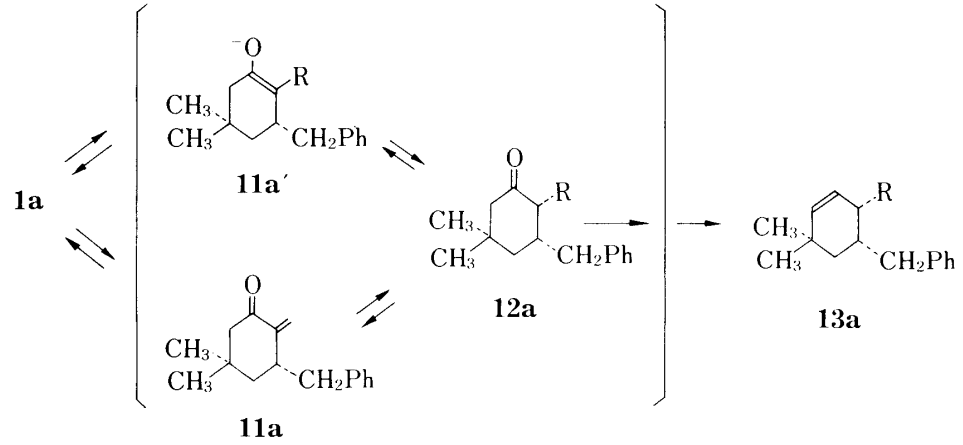


Chart 3

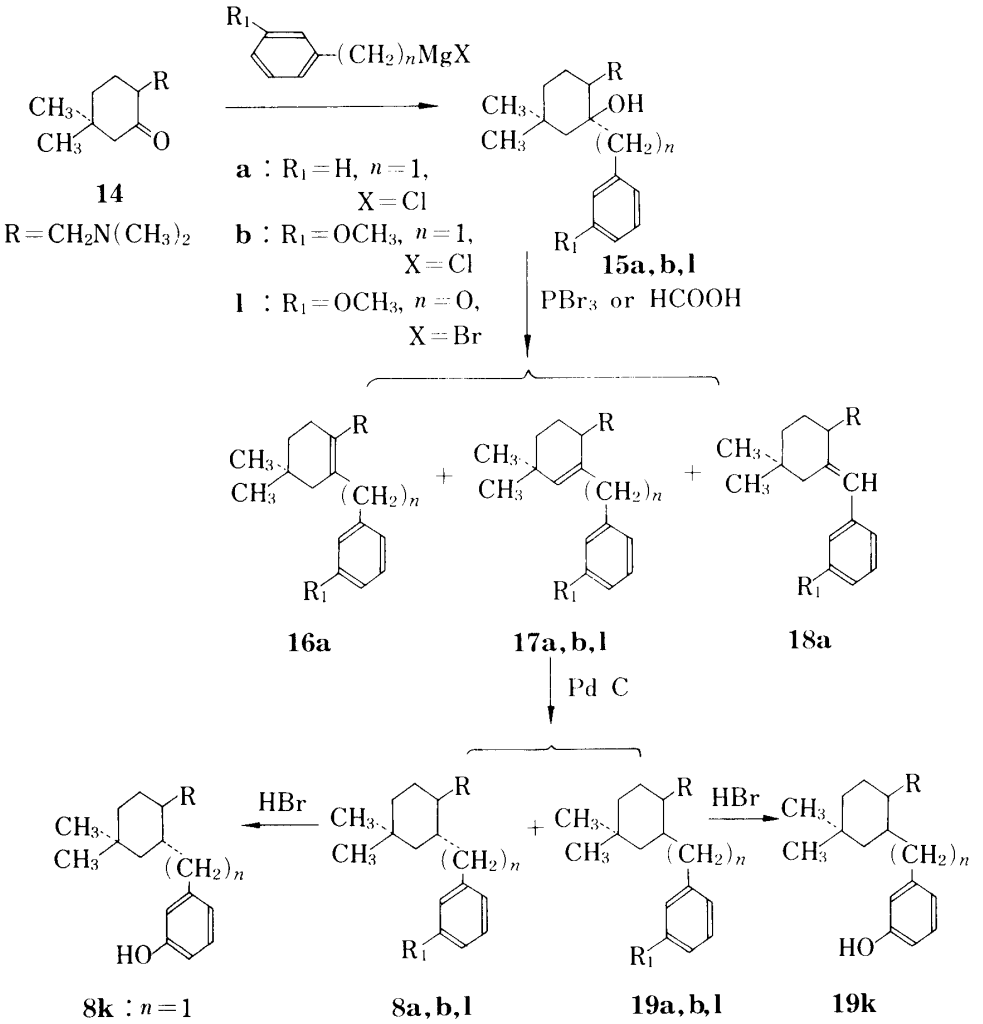


Chart 4

Synthesis of 1,2-*trans*- and 1,2-*cis*-*N*,*N*-Dimethyl-[2-(substituted)benzyl (and phenyl)-4,4-dimethylcyclohexyl]methylamines (8 and 19)

Although, 1,2-*trans*- and 1,2-*cis*-cyclohexylmethylamines (**8** and **19**) were expected to be produced by the catalytic reduction of the corresponding (2-cyclohexenyl)methylamines (**5** and **13**), this route was abondoned because of the poor yields of **5** and **13**. Another route shown in Chart 4 was therefore investigated.

The starting compound, 1-benzyl-*c*-2-dimethylaminomethyl-5,5-dimethyl-*r*-1-cyclohexanol (**15a**), was prepared by the Grignard reaction between benzylmagnesium chloride and 2-dimethylaminomethylcyclohexanone (**14**), which was obtained by the Mannich reaction of 3,3-dimethylcyclohexanone.[9] Treatment of **15a** with phosphorus tribromide (PBr_3)[10] in benzene, followed by distillation of the resulting crude oil *in vacuo* in the presence of potassium hydroxide gave a mixture of olefinic compounds, from which **16a** (2.2%), **17a** (19%), and **18a** (0.8%) were isolated as the hydrochlorides. Catalytic reduction of **17a** with palladium carbon (Pd-C) in acetic acid followed by treatment with hydrochloric acid afforded the 1,2-*cis*-cyclohexylmethylamine (**19a**) and the 1,2-*trans*-cyclohexylmethylamine (**8a**) hydro-

TABLE III. 1,2-*trans* and 1,2-*cis*-Cyclohexylmethylamines (**8** and **19**) and Related Compounds

Compd.	mp (°C)	Recrystn. solvent[a]	Yield (%)	Formula	Analysis (%) Calcd (Found)		
					C	H	N
15a	241—242	A	48[d]	$C_{18}H_{29}NO \cdot HCl \cdot 3/4H_2O$	66.42 (66.54)	9.78 9.35	4.30 4.13)
15b	243—244	B	40[d]	$C_{19}H_{31}NO_2 \cdot HCl$	66.74 (66.63)	9.43 9.59	4.10 4.23)
15l	93—96	—[b]	24[d]	$C_{18}H_{29}NO_2 \cdot HCl$	65.02 (65.12)	9.27 9.09	4.21 4.05)
16a	204—205	C	2.2[e]	$C_{18}H_{27}N \cdot HCl \cdot 1/4H_2O$	72.46 (72.33)	9.63 9.69	4.69 4.46)
17a	233—235	D	19[e]	$C_{18}H_{27}N \cdot HCl$	73.57 (73.54)	9.60 9.67	4.77 4.81)
17l	185—186	B	51[e]	$C_{18}H_{27}NO \cdot HCl$	69.77 (69.39)	9.11 9.35	4.52 4.41)
8a	198—200	C	51[f]	$C_{18}H_{29}N \cdot HCl$	73.04 (73.08)	10.25 10.23	4.73 4.67)
8b	177—179	B	28[e]	$C_{19}H_{31}NO \cdot HCl$	70.02 (69.75)	9.90 9.92	4.30 4.45)
8k	200—202	B	76[g]	$C_{18}H_{29}NO \cdot HCl$	69.30 (69.23)	9.72 9.92	4.49 4.40)
8l	225—226	B	71[f]	$C_{18}H_{29}NO \cdot HCl$	69.30 (69.46)	9.72 9.80	4.49 4.62)
19a	237—239	C	12[f]	$C_{18}H_{29}N \cdot HCl$	73.04 (73.03)	10.25 10.64	4.73 4.74)
19b	180—182	B	6.5[e]	$C_{19}H_{31}NO \cdot HCl$	70.02 (69.87)	9.90 9.97	4.30 4.43)
19l	204—206	C	9.4[f]	$C_{18}H_{29}NO \cdot HCl$	69.30 (69.29)	9.72 9.87	4.49 4.45)
19k	203—205	B	61[g]	$C_{18}H_{29}NO \cdot HCl$	69.30 (69.09)	9.72 9.77	4.49 4.79)

a) A = EtOH; B = AcOEt–MeOH; C = Me_2CO; D = EtOH–Me_2CO.
b) Powder.
c) Decomposition.
d)—*g*) Calculated from **14**, **15**, **17** and the corresponding methoxy derivatives, respectively.

chlorides in 12 and 51% yields, respectively. The **8a** hydrochloride obtained was identical with the sample obtained from **5a**, which has 1,2-*trans* stereochemistry.

1,2-*trans*- and 1,2-*cis*-*N*,*N*-Dimethyl-[4,4-dimethyl-2-(3-methoxybenzyl)cyclohexyl]-methylamine (**8b** and **19b**) hydrochlorides were similarly obtained from **15b**. The Grignard reaction of **14** with 3-methoxyphenylmagnesium bromide gave **15l**, which was dehydrated with formic acid to yield **17l**.[11] The catalytic reduction of **17l** followed by purification as the hydrochlorides gave 1,2-*trans*- and 1,2-*cis*-*N*,*N*-dimethyl-[4,4-dimethyl-2-(3-methoxyphenyl)-cyclohexyl]methylamine (**8l** and **19l**) hydrochlorides in 71 and 9.4% yields, respectively.

The methoxy derivatives (**8b** and **19b**) were treated with hydrobromic acid to give the phenolic derivatives (**8k** and **19k**).

The compounds synthesized in this report were tested for analgesic activities by using the phenylquinone writhing method in mice. Compound **5a** showed analgesic activity as potent as that of codeine phosphate. The pharmacological data will be reported in detail elsewhere.

Experimental

All melting points were taken in open capillaries and are uncorrected. IR spectra and mass spectra were measured on Hitachi EPI-S2 and RMS-4 machines, respectively. NMR spectra were recorded on a Hitachi R-20 spectrometer using tetramethylsilane as an internal standard.

Dehydration of *t*-3-Benzyl-*c*-2-dimethylaminomethyl-5,5-dimethyl-*r*-1-cyclohexanol (2a) with $SOCl_2$——$SOCl_2$ (1.0 g, 8.4 mmol) was added to a solution of **2a** (1.0 g, 3.6 mmol) in CH_2Cl_2 (10 ml) with stirring and the solution was refluxed for 2 h. The solvent was evaporated off, and AcOEt was added to the resulting residue. The precipitated solid was collected by filtration and recrystallized from MeOH to give *N*,*N*-dimethyl-(6-benzyl-4,4-dimethyl-1-cyclohexenyl)methylamine (**4a**)·HCl as colorless plates (0.40 g, 38%), mp 220—222 °C (dec.). IR ν_{max}^{KBr} cm^{-1}: 1655 (C=C). **4a**: NMR ($CDCl_3$) δ: 0.78, 0.85 (each 3H, s, C_4-CH_3), 1.78 (2H, m, C_3-H_2), 2.19 (6H, s, $N(CH_3)_2$), 2.45 (2H, d, J=11 Hz, C_6-CH_2), 3.24, 3.43 (each 1H, m, C_1-CH_2-N), 5.57 (1H, m, C_2-H), 7.21 (5H, s, C_6H_5). MS *m/e*: 257 (M^+). *Anal.* Calcd for $C_{18}H_{27}N \cdot HCl \cdot 1/5H_2O$: C, 72.68; H, 9.62; N, 4.71. Found: C, 72.84; H, 9.59; N, 4.57. The filtrate of recrystallization was concentrated to dryness *in vacuo*. AcOEt was added to the resulting residue. The precipitated solid was collected by filtration and heated in acetone. The insoluble solid was filtered off and the filtrate was allowed to stand at room temperature to give 1,6-*trans*-*N*,*N*-dimethyl-(6-benzyl-4,4-dimethyl-2-cyclohexenyl)methylamine (**5a**)·HCl (0.15 g, 14%) as colorless needles, mp 187—189 °C. IR ν_{max}^{KBr} cm^{-1}: 1650 (C=C). **5a**: NMR ($CDCl_3$) δ: 0.82, 0.90 (each 3H, s, C_4-CH_3), 2.22 (6H, s, $N(CH_3)_2$), 3.08 (1H, dd, J=3 and 13 Hz, C_1-C$\overset{H}{\underset{H}{<}}$), 5.43 (1H, d, J=10 Hz, C_2-H), 5.67 (1H, d, J=10 Hz, C_3-H), 7.0—7.4 (5H, m, C_6H_5). MS *m/e*: 257 (M^+), 212, 198, 105, 91. *Anal.* Calcd for $C_{18}H_{27}N \cdot HCl \cdot 1/3H_2O$: C, 72.09; H, 9.63; N, 4.67. Found: C, 72.11; H, 9.43; N, 4.34. All the filtrates were combined and concentrated to dryness *in vacuo*. H_2O was added to the resulting residue and the aqueous solution was basified with 10% aqueous NH_4OH and extracted with ether. The extract was washed with H_2O, dried over K_2CO_3 and concentrated *in vacuo* to give a pale yellowish oil (0.3 g). Chromatography of this oil on a silica gel column (5 g) using C_6H_6–AcOEt (10:1) as an eluent yielded *N*,*N*-dimethyl-(*t*-6-benzyl-*t*-2-chloro-4,4-dimethyl-*r*-1-cyclohexyl)methylamine (**6a**) as a colorless oil (0.19 g, 18%). NMR ($CDCl_3$) δ: 0.80, 0.87 (each 3H, s, C_4-CH_3), 2.69 (2H, d, J=4 Hz, C_6-CH_2), 3.40 (1H, octet, J=5, 11, and 12 Hz, C_2-H), 7.20 (5H, m, C_6H_5). 1 N HCl (1 ml) was added to a solution of **6a** in EtOH (4 ml) and the mixture was concentrated to dryness *in vacuo*. The resulting residue was recrystallized from AcOEt–MeOH to give **6a**·HCl as colorless needles, mp 168—170 °C. *Anal.* Calcd for $C_{18}H_{28}ClN \cdot HCl$: C, 65.45; H, 8.85; N, 4.24. Found: C, 65.29; H, 9.08; N, 4.19.

Dehydration of *c*-3-Benzyl-*t*-2-dimethylaminomethyl-5,5-dimethyl-*r*-1-cyclohexanol (3a) with $SOCl_2$——$SOCl_2$ (12.6 g, 0.11 mol) was added to a solution of **3a** (14.5 g, 53 mmol) in CH_2Cl_2 (40 ml) and the mixture was refluxed for 3.5 h with stirring. The solvent was evaporated off, and AcOEt was added to the residue. The precipitated solid was collected by filtration and recrystallized from acetone to give **5a**·HCl as colorless needles (8.2 g, 53%), mp 187—189 °C. The combined filtrates were concentrated to dryness *in vacuo* and treated as described in the preceding section to give *N*,*N*-dimethyl-(*t*-6-benzyl-*c*-2-chloro-4,4-dimethyl-*r*-1-cyclohexyl)methylamine (**7a**) as a solid (3.0 g, 19%) and additional **5a** as a colorless oil (3.0 g, 22%). The solid (**7a**) was recrystallized from hexane to give colorless prisms, mp 65—67 °C. NMR ($CDCl_3$) δ: 0.85, 1.06 (each 3H, s, C_4-CH_3), 2.23 (6H, s, $N(CH_3)_2$), 3.08 (1H, dd, J=9 and 18 Hz, C_1-C$\overset{H}{\underset{H}{>}}$), 4.65 (1H, q, J=4 Hz, C_2-H), 7.0—7.4 (5H, m, C_6H_5). *Anal.* Calcd for $C_{18}H_{28}ClN$: C, 73.57; H, 9.60; N, 4.77. Found: C, 73.53; H, 9.90; N, 4.53.

General Procedure for Preparing (2-Cyclohexenyl)methylamines (5)——A solution of 2-aminomethyl-3-benzylcyclohexanone (**1**)[1] (20 mmol) in dry ether (30 ml) was added dropwise to a suspension of $LiAlH_4$ (1.0 g,

27 mmol) in dry ether (10 ml) with stirring and cooling, and the mixture was refluxed for 1.5 h. Hydrolysis was effected by the dropwise addition of H_2O under ice-cooling. The ethereal layer was separated and the aqueous mixture was extracted with ether. The combined ethereal solutions were washed with H_2O, dried over K_2CO_3 and concentrated *in vacuo* to give a mixture of 1,2-*trans*- and 1,2-*cis*-cyclohexanols (**2** and **3**). $SOCl_2$ (44 mmol) was added to a solution of the mixture in CH_2Cl_2 (15 ml) with stirring and the solution was refluxed for 3.5 h. The solvent was evaporated off, and H_2O was added to the resulting residue. The separated oil was extracted with ether. The aqueous solution was basified with ammonia water and extracted with ether. The extract was washed with H_2O, dried over K_2CO_3, and concentrated *in vacuo* to give a crude oil, which was chromatographed on a silica gel (35 g) column using a mixture of C_6H_6–AcOEt as the eluent to yield **5** as an oil. 1 N HCl (1.5 × the calculated amount) was added to a solution of **5** in EtOH and the solution was concentrated to dryness *in vacuo*. The resulting residue was recrystallized to give **5**·HCl as colorless crystals (Tables II, IV).

When **3**, instead of a mixture of **2** and **3**, was used as a starting material, it was treated with $SOCl_2$ as described above.

1,2-*trans*-*N*,*N*-Dimethyl-(2-benzyl-4,4-dimethylcyclohexyl)methylamine (8a)——A suspension of **5a**·HCl (0.7 g, 2.4 mmol) and 5% Pd-C (50% wet) (0.4 g) in MeOH (20 ml) was shaken under a hydrogen atmosphere at room

TABLE IV. Physical Data for 2-Cyclohexenylmethylamines (**5**)

Compd.	IR ν_{max}^{KBr} cm^{-1} [a] C=C	NMR ($CDCl_3$) δ
5b	1645	0.88, 0.94 (each 3H, s, C_4–CH_3), 2.27 (6H, s, $N(CH_3)_2$), 3.06 (1H, dd, J=3, 13 Hz, C_1–C<H/H), 3.76 (3H, s, OCH_3), 5.40, 5.66 (each 1H, d, J=9 Hz, C_2–H, C_3–H)
5c	1655	0.81, 0.90 (each 3H, s, C_4–CH_3), 2.24 (6H, s, $N(CH_3)_2$), 2.31 (3H, s, CH_3), 3.0—3.3 (1H, m, C_1–C<H/H), 5.40, 5.69 (each 1H, d, J=10 Hz, C_2–H, C_3–H)
5d	1645	0.79, 0.92 (each 3H, s, C_4–CH_3), 2.17 (6H, s, $N(CH_3)_2$), 3.22 (1H, dd, J=3, 13 Hz, C_1–C<H/H), 5.40, 5.64, (each 1H, d, J=10 Hz, C_2–H, C_3–H)
5e	1650	0.83, 0.92 (each 3H, s, C_4–CH_3), 3.12 (1H, dd, J=3, 13 Hz, C_1–C<H/H), 5.45, 5.60 (each 1H, d, J=11 Hz, C_2–H, C_3–H)
5f	1670	0.79, 0.92 (each 3H, s, C_4–CH_3), 3.28 (1H, complex d, J=14 Hz, C_1–C<H/H), 5.40, 5.65 (each 1H, d, J=9 Hz, C_2–H, C_3–H)
5g	1655	0.79, 0.88 (each 3H, s, C_4–CH_3), 3.07 (1H, dd, J=3, 13 Hz, C_1–C<H/H), 5.36, 5.59 (each 1H, d, J=11 Hz, C_2–H, C_3–H)
5h	1650	0.80, 0.90 (each 3H, s, C_4–CH_3), 3.06 (1H, dd, J=4, 14 Hz, C_1–C<H/H), 3.70 (4H, t, J=5 Hz, CH_2–O–CH_2), 5.33, 5.59 (each 1H, d, J=10 Hz, C_2–H, C_3–H)
5i	1655 [b]	0.76, 0.87 (each 3H, s, C_4–CH_3), 2.16 (3H, s, N–CH_3), 3.06 (1H, dd, J=3, 13 Hz, C_1–C<H/H), 3.28, 3.57 (each 1H, AB type q, J=14 Hz, N–CH_2–Ph), 5.33, 5.68 (each 1H, d, J=10 Hz, C_2–H, C_3–H)
5j	1650	0.82, 0.90 (each 3H, s, C_4–CH_3), 2.27 (3H, s, N–CH_3), 3.06 (1H, dd, J=3, 13 Hz, C_1–C<H/H), 5.30, 5.55 (each 1H, d, J=11 Hz, C_2–H, C_3–H)
5l	1650	1.03 (6H, s, $C_4(CH_3)_2$), 2.52 (6H, s, $N(CH_3)_2$), 2.4—2.8 (2H, m, C_1–CH_2–N), 3.76 (3H, s, OCH_3), 5.61, 6.03 (each 1H, d, J=9 Hz, C_2–H, C_3–H)

a) Hydrochloride. b) Hydrobromide.

temperature and 54 ml of H_2 was absorbed. The catalyst was filtered off and the filtrate was concentrated *in vacuo*. AcOEt was added to the residue. The precipitated solid was collected by filtration and recrystallized from AcOEt–MeOH to give **8a**·HCl as colorless needles (0.50 g, 70%), mp 198—200 °C. **8a**: NMR ($CDCl_3$) δ: 0.76, 0.82 (each 3H, s, C_4–CH_3), 2.22 (6H, s, $N(CH_3)_2$), 3.15 (1H, dd, J=3 and 12 Hz, C_1–C$\lesssim^{H}_{H}$), 7.0—7.4 (5H, m, C_6H_5). *Anal.* Calcd for $C_{18}H_{29}N$·HCl: C, 73.04; H, 10.25; N, 4.73. Found: C, 73.08; H, 10.23; N, 4.67.

1,6-*cis*-*N*,*N*-Dimethyl-(6-benzyl-4,4-dimethyl-2-cyclohexenyl)methylamine (13a)——A mixture of 2,3-*trans*-3-benzyl-2-dimethylaminomethyl-5,5-dimethylcyclohexanone (**1a**)·HCl (2.0 g, 6.5 mmol), 40% dimethylamine solution (0.8 g), H_2O (10 ml) and EtOH (20 ml) was refluxed for 9 h with stirring, then cooled. NaOH (0.4 g) and $NaBH_4$ (0.48 g) were added to the solution and the mixture was stirred for 1 h at room temperature. The solvent was evaporated off, and H_2O was added to the residue. The separated oil was extracted with ether. The extract was washed with H_2O, dried over K_2CO_3, and concentrated *in vacuo* to give a crude oil (1.7 g). $SOCl_2$ (1.2 ml) was added to a solution of this oil in CH_2Cl_2 (16 ml) and the mixture was refluxed for 5 h with stirring. The solvent was evaporated off, and the resulting residue was treated as described in the general procedure for preparing **5** to give a crude oil (1.7 g), which was chromatographed on an alumina (40 g) column using hexane–C_6H_6 (10 : 1) as an eluent to yield **13a** as a yellowish oil (0.20 g, 12%). NMR ($CDCl_3$) δ: 0.88, 0.96 (each 3H, s, C_4–CH_3), 2.18 (6H, s, $N(CH_3)_2$), 2.25 (2H, d, J=4 Hz, C_6–CH_2), 2.4—2.8 (2H, m, C_1–CH_2), 5.42 (1H, d, J=10 Hz, C_3–H), 5.75 (1H, complex d, J=*ca.* 10 Hz, C_2–H), 7.2—7.4 (5H, m, C_6H_5). 1 N HCl (1 ml) was added to a solution of this oil in EtOH (5 ml) and the mixture was concentrated to dryness *in vacuo*. The resulting residue was recrystallized from AcOEt–MeOH to give **13a**·HCl as colorless needles (0.15 g, 8%), mp 209—211 °C. IR ν_{max}^{KBr} cm^{-1}: 1645 (C=C). *Anal.* Calcd for $C_{18}H_{27}N$·HCl·1/3H_2O: C, 72.09; H, 9.64; N, 4.67. Found: C, 71.99; H, 9.63; N, 4.64. MS *m/e*: 257 (M^+), 212, 198, 105, 91.

2-Dimethylaminomethyl-5,5-dimethylcyclohexanone (14)——A mixture of 3,3-dimethylcyclohexanone[10] (17.4 g, 0.14 mol), $HN(CH_3)_2$·HCl (11.3 g), paraformaldehyde (5.2 g), one drop of conc. HCl, and EtOH (60 ml) was refluxed for 6.5 h with stirring. The solvent was evaporated off, and AcOEt was added to the residue. The precipitated solid was collected by filtration and recrystallized from AcOEt–MeOH to give **14**·HCl as colorless needles (15.7 g, 50%), mp 142—144 °C. IR ν_{max}^{KBr} cm^{-1}: 1700 (C=O). **14**: NMR (CCl_4) δ: 0.87, 1.00 (each 3H, s, C_5–CH_3), 2.10 (2H, s, C_6–H_2), 2.15 (6H, s, $N(CH_3)_2$). *Anal.* Calcd for $C_{11}H_{21}NO$·HCl: C, 60.12; H, 10.09; N, 6.37. Found: C, 59.97; H, 10.22; N, 6.57.

1-Benzyl-*c*-2-dimethylaminomethyl-5,5-dimethyl-*r*-1-cyclohexanol (15a)——A solution of **14** (45.0 g, 0.25 mol) in dry ether (70 ml) was added to the Grignard reagent prepared from Mg turnings (12.0 g) and benzyl chloride (62.1 g) in dry ether (370 ml), and the mixture was refluxed for 4 h. Hydrolysis was effected by the dropwise addition of a saturated NH_4Cl solution under ice-cooling. The ethereal layer was separated and the aqueous mixture was extracted with ether. The combined ethereal solutions were washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give a pale yellowish oil (60.5 g). Conc. HCl (2.1 g) was added to a solution of this oil (5.4 g) in EtOH (50 ml) and the mixture was concentrated to dryness *in vacuo*. AcOEt was added to the residue. The precipitated solid was collected by filtration and recrystallized from AcOEt–MeOH to give **15a**·HCl as colorless needles (3.5 g, 48%), mp 241—242 °C. IR ν_{max}^{KBr} cm^{-1}: 3400 (OH). **15a**: NMR ($CDCl_3$) δ: 0.89, 1.03 (each 3H, s, C_5–CH_3), 2.27 (6H, s, $N(CH_3)_2$), 2.65 (2H, d, J=5 Hz, C_2–CH_2), 2.67, 3.07 (each 1H, AB type q, J_{AB}=13 Hz, C_1–CH_2), 4.90 (1H, m, OH), 7.28 (5H, s, C_6H_5).

***N*,*N*-Dimethyl-(2-benzyl-4,4-dimethyl-1- and 2-cyclohexenyl)methylamines (16a and 17a) and *N*,*N*-Dimethyl-(2-benzylidene-4,4-dimethylcyclohexyl)methylamine (18a)**——A solution of PBr_3 (35.4 g, 0.13 mol) in C_6H_6 (110 ml) was added dropwise to a solution of **15a** (55.1 g, 0.20 mol) in C_6H_6 (110 ml) with stirring and ice-cooling, and the mixture was stirred for 4 h at 0—5 °C. H_2O was added to the reaction mixture and the mixture was basified with ammonia water. The separated C_6H_6 layer was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give a brownish oil (55 g), which was distilled with KOH (10 g) *in vacuo* to give a yellowish oil (37.1 g), bp 110—122 °C (0.3 mmHg), and **15a** (9.9 g), bp 130—137 °C (0.3 mmHg). The yellowish oil (18.6 g) was chromatographed on an alumina (350 g) column using C_6H_6 as an eluent to give a mixture (16 g) of **16a** and **17a** (1 : 2), as well as **15a** (1.9 g). Conc. HCl (8.0 g) was added to a solution of the mixture in EtOH (60 ml) and the solution was concentrated to dryness *in vacuo*. AcOEt was added to the residue. The precipitated solid was collected by filtration and recrystallized from acetone–EtOH to give **17a**·HCl as colorless needles (5.6 g, 19%), mp 233—235 °C. IR ν_{max}^{KBr} cm^{-1}: 1665 (C=C). **17a**: NMR ($CDCl_3$) δ: 0.98 (6H, s, C_4–CH_3), 2.50 (6H, s, $N(CH_3)_2$), 2.30 (2H, s, C_2–CH_2), 5.33 (1H, s, CH_3–H), 6.80—7.35 (5H, m, C_6H_5). The above filtrate (AcOEt solution) was concentrated to dryness *in vacuo*. AcOEt was added to the residue. The precipitated solid was collected by filtration and recrystallized from acetone to give **16a**·HCl as colorless needles (0.65 g, 2.2%), mp 204—205 °C. IR ν_{max}^{KBr} cm^{-1}: 1665 (C=C). **16a**: NMR ($CDCl_3$) δ: 0.83 (6H, s, C_4–CH_3), 2.19 (6H, s, $N(CH_3)_2$), 2.96 (2H, s, C_1–CH_2), 3.45 (2H, s, C_2–H_2), 7.0—7.4 (5H, m, C_6H_5). The filtrate after removal of **16a**·HCl (AcOEt solution) gave, on standing, **18a**·HCl as colorless needles (30 mg, 0.1%), mp 218—221 °C. IR ν_{max}^{KBr} cm^{-1}: 1650 (C=C). **18a**: NMR ($CDCl_3$) δ: 0.82 (6H, s, C_4–CH_3), 2.23 (6H, s, $N(CH_3)_2$), 2.10 (2H, s, C_3–H_2), 6.43 (1H, s, CH=C), 7.0—7.4 (5H, m, C_6H_5). *Anal.* Calcd for $C_{18}H_{27}N$·HCl: C, 73.57; H, 9.60; N, 4.77. Found: C, 73.41; H, 9.75; N, 4.63.

1,2-*trans*- and 1,2-*cis*-*N*,*N*-Dimethyl-(2-benzyl-4,4-dimethylcyclohexyl)methylamines (8a and 19a)——A suspen-

sion of **17a** (3.6 g, 14 mmol), 5% Pd-C (50% wet) (1.6 g) and AcOH (35 ml) was shaken under a hydrogen atmosphere at 60—70 °C. When the absorption of H_2 had ceased, the catalyst was filtered off and the filtrate was concentrated *in vacuo*. A solution of the residue in 5% HCl (20 ml) was washed with ether, basified with ammonia water, and extracted with ether. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give a pale yellowish oil (3.1 g). Conc. HCl (1.3 g) was added to a solution of this oil in EtOH (20 ml) and the mixture was concentrated to dryness *in vacuo*. AcOEt was added to the residue and the precipitated solid was collected by filtration and recrystallized from acetone to give **19a**·HCl as colorless plates (0.5 g, 12%), mp 237—239 °C. **19a**: NMR ($CDCl_3$) δ: 0.86, 0.89 (each 3H, s, C_4–CH_3), 2.15 (6H, s, $N(CH_3)_2$), 2.4—2.7 (2H, m, C_1–CH_2), 7.0—7.3 (5H, m, C_6H_5). The filtrate was concentrated to dryness *in vacuo*. AcOEt was added to the resulting residue. The precipitated solid was collected by filtration and recrystallized from acetone to give **8a**·HCl as colorless needles (2.1 g, 51%), mp 198—200 °C.

***c*-2-Dimethylaminomethyl-1-(3-methoxybenzyl)-5,5-dimethyl-*r*-1-cyclohexanol (15b)**——A solution of **14** (10.2 g, 56 mmol) in dry ether (20 ml) was added dropwise to the Grignard reagent prepared from Mg turnings (2.1 g) and 3-methoxybenzyl chloride (14.3 g, 91 mmol) in dry ether (60 ml). The mixture was refluxed for 4 h and treated as described for the preparation of **15a** to give a yellowish oil (10.3 g), which was chromatographed on a silica gel (100 g) column using C_6H_6–AcOEt (1 : 1) as an eluent to yield **15b** as a yellowish oil (8.4 g). 1 N HCl (30 ml) was added to a solution of this oil in EtOH (40 ml) and the mixture was concentrated to dryness *in vacuo*. The residue was recrystallized from AcOEt–MeOH to give **15b**·HCl as colorless needles (7.4 g, 40%), mp 243—244 °C (Tables III, V).

1,2-*trans*- and 1,2-*cis*-*N*,*N*-Dimethyl-[2-(3-methoxybenzyl)-4,4-dimethylcyclohexyl]methylamines (8b and 19b)——A solution of PBr_3 (4.2 g) in C_6H_6 (13 ml) was added dropwise to a solution of **15b** (7.2 g, 24 mmol) in C_6H_6 (15 ml) with stirring and ice-cooling, and the mixture was treated as described for the preparation of **17a** to give a mixture of **15b**, **16b**, and **17b** as a yellowish oil (7.0 g). A suspension of this oil, 5% Pd-C (50% wet) (5.0 g), and AcOH (75 ml) was shaken under a hydrogen atmosphere at 60—70 °C, and treated as described for the preparation of **8a** and **19a** to give a yellowish oil (4.0 g), which was chromatographed on an alumina (55 g) column using C_6H_6–hexane (1 : 5) as an eluent to yield a mixture of **8b** and **19b** as a yellowish oil (3.5 g). Conc. HCl (1.9 g) was added to a solution of this oil in EtOH (40 ml) and the mixture was concentrated to dryness *in vacuo*. AcOEt was added to the residue. The precipitated solid was collected by filtration and recrystallized from AcOEt–MeOH to give **8b**·HCl as colorless needles (2.2 g, 28%), mp 177—179 °C. The filtrate was allowed to stand at room temperature to give crystals, which were recrystallized from AcOEt–MeOH to give **19b**·HCl as colorless needles (0.51 g, 6.5%), mp 180—182 °C (Tables III, V).

***c*-2-Dimethylaminomethyl-1-(3-methoxyphenyl)-5,5-dimethyl-*r*-1-cyclohexanol (15l)**——A solution of **14** (5.8 g, 32 mmol) in dry ether (15 ml) was added dropwise to the Grignard reagent prepared from Mg turnings (1.55 g) and *m*-bromoanisole (11.8 g, 63 mmol) in dry ether (50 ml), and the mixture was refluxed for 3 h with stirring. The reaction mixture was treated as described for the preparation of **15a** to give a yellowish oil (3.1 g). Oxalic acid ($2H_2O$) (1.1 g) was added to a solution of this oil (2.5 g) in EtOH (5 ml) and the solution was concentrated to dryness *in vacuo*. The resulting residue was recrystallized from AcOEt–MeOH to give **15l** oxalate as colorless crystals (2.5 g), mp 156—160 °C. The oxalate was converted to a colorless oil (1.9 g) (free base) by the usual method. Conc. HCl (0.7 g) was added to a solution of this oil in EtOH (15 ml) and the mixture was concentrated to dryness *in vacuo* to give **15l**·HCl as an amorphous material (2.0 g, 24%), mp 93—96 °C (Tables III, V).

***N*,*N*-Dimethyl-[2-(3-methoxyphenyl)-4,4-dimethyl-2-cyclohexenyl]methylamine (17l)**——A solution of **15l** (22 g, 76 mmol) in 99% formic acid was refluxed for 4 h with stirring. The formic acid was evaporated off, and H_2O was added to the residue. The aqueous solution was basified with ammonia water and extracted with ether. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated *in vacuo* to give a brownish oil (20 g), which was similarly converted to its hydrochloride by treatment with conc. HCl (9.8 g). The crude crystals of the hydrochloride, obtained in the usual manner were recrystallized from AcOEt–MeOH to give **17l**·HCl as colorless needles (11.9 g, 51%), mp 185—186 °C (Tables III, V).

1,2-*trans*- and 1,2-*cis*-*N*,*N*-Dimethyl-[2-(3-methoxyphenyl)-4,4-dimethylcyclohexyl]methylamines (8l and 19l)——A suspension of **17l**·HCl (7.5 g, 24 mmol), 5% Pd-C (50% wet) (2.0 g) and MeOH (50 ml) was shaken under a hydrogen atmosphere. When the absorption of H_2 had ceased, the catalyst was filtered off and the filtrate was concentrated to dryness *in vacuo*. AcOEt was added to the residue. The precipitated solid was collected by filtration and recrystallized twice from AcOEt–MeOH to give **8l**·HCl as colorless needles (5.3 g, 71%), mp 225—226 °C. The combined filtrates were concentrated to dryness *in vacuo*. A solution of the residue in acetone was allowed to stand at room temperature to give colorless crystals, which were recrystallized from acetone to give **19l**·HCl as colorless needles (0.7 g, 9.4%), mp 204—206 °C (Tables III, V).

1,2-*trans*-*N*,*N*-Dimethyl-[2-(3-hydroxybenzyl)-4,4-dimethylcyclohexyl]methylamine (8k)——A mixture of **8b**·HCl (1.5 g, 4.6 mmol) and 47% aqueous HBr (16 ml) was stirred for 2 h at 130—140 °C. H_2O was added to the reaction mixture and the aqueous mixture was basified with ammonia water and extracted with C_6H_6. The extract was washed with H_2O, dried over $MgSO_4$, and concentrated to dryness *in vacuo* to give **8k** as yellowish crystals (1.1 g), mp 97—100 °C. This product was similarly converted to its hydrochloride. The solid hydrochloride obtained in the usual manner was recrystallized from AcOEt–MeOH to give **8k**·HCl as pale yellowish needles (1.1 g, 77%), mp 200—

TABLE V. Physical Data for Cyclohexylmethylamines (**8** and **19**) and Related Compounds

Compd.	IR ν_{max}^{KBr} cm^{-1} [a]	NMR ($CDCl_3$) δ
15b	3400 (OH)	0.84, 0.98 (each 3H, s, C_5–CH_3), 2.23 (6H, s, $N(CH_3)_2$), 2.60 (2H, d, J=5 Hz, C_2–CH_2), 2.59, 2.99 (each 1H, AB type q, J_{AB}=13 Hz, C_1–CH_2), 3.77 (3H, s, OCH_3)
15l	3400 (OH)	0.85, 1.23 (each 3H, s, C_5–CH_3), 2.42, 2.68 (each 3H, s, N–CH_3), 3.06 (1H, s, OH), 3.81 (3H, s, OCH_3)
17l	1640 (C=C)	1.17, 1.22 (each 3H, s, C_4–CH_3), 2.59 (6H, s, $N(CH_3)_2$), 3.91 (3H, s, OCH_3), 5.78 (1H, s, C_3–H), 7.39 (1H, br s, OH)
8b		0.76, 0.89 (each 3H, s, C_4–CH_3), 2.57 (6H, s, $N(CH_3)_2$), 2.90, 3.10 (each 1H, br s, C_1–CH_2–N), 3.71 (3H, s, OCH_3)
8k	3150 (OH)	0.80, 0.85 (each 3H, s, C_4–CH_3), 2.26 (6H, s, $N(CH_3)_2$), 3.10 (1H, complex d, J=13 Hz, C_1–C<H/H–N)
8l		1.07, 1.11 (each 3H, s, C_4–CH_3), 2.50 (6H, s, $N(CH_3)_2$), 3.88 (3H, s, OCH_3)
19b		0.86 (6H, s, $C_4(CH_3)_2$), 2.15 (6H, s, $N(CH_3)_2$), 3.72 (3H, s, OCH_3)
19k	3180 (OH)	0.95 (6H, s, $C_4(CH_3)_2$), 2.10 (6H, s, $N(CH_3)_2$)
19l		0.97 (6H, s, $C_4(CH_3)_2$), 2.08 (6H, s, $N(CH_3)_2$), 3.76 (3H, s, OCH_3)

a) Hydrochloride.

202 °C.

Compound **19k** was also obtained by a similar procedure (Tables III, V).

Acknowledgement The authors are grateful to Drs. E. Ohmura, K. Morita, and Y. Sanno for encouragement and helpful advice throughout this work.

References and Notes

1) T. Kato, T. Hattori, K. Kawai, and Y. Sawa, *Chem. Pharm. Bull.*, **31**, 3915 (1983).
2) M. Herrmann, W. Steinbrecher, and W. Heldt, *Arzneim.-Forsch.*, **20**, 977 (1970).
3) A. Saytzeff, *Justus Liebigs Ann. Chem.*, **179**, 296 (1875).
4) Dehydrochlorination of menthyl chloride is known to afford 2-menthene: *a*) W. Huckel, W. Tappe, and G. Legutke, *Justus Liebigs Ann. Chem.*, **543**, 191 (1940); *b*) E. D. Hughes, C. K. Ingold, and J. B. Rose, *J. Chem. Soc.*, **1953**, 3839.
5) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henry Holt and Company, Inc., New York, 1959, pp. 294—295.
6) *a*) H. Schaeffer and C. J. Collins, *J. Am. Chem. Soc.*, **78**, 124 (1956); *b*) H. L. Goering, R. L. Reeve, and H. H. Epsy, *ibid.*, **78**, 4926 (1956).
7) J. B. Wright, *J. Org. Chem.*, **25**, 1867 (1960).
8) K. Biemann, "Mass Spectrometry," McGraw-Hill, New York, 1962, p. 144.
9) A. W. Allan, R. P. A. Sneeden, and J. M. Wilson, *J. Chem. Soc.*, **1969**, 2186.
10) A similar reaction is known: J. Frejka and J. Dvorak, *Chem. Listy*, **46**, 684 (1952) [*Chem. Abstr.*, **47**, 8025*g* (1953)].
11) A. L. Morrison and H. Rinderknecht, *J. Chem. Soc.*, **1950**, 1510.